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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 08/838,486
Filing Date: April 07, 1997
Appellant(s): BAEKKESKOV ET AL.

Joe Liebeschuetz
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 8/14/06 appealing from the Office action mailed 7/29/03.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Applicant has requested an interference be declared between the instant application and U.S. Patent Nos. 6,001,360 and 5,762,937.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The Appellant's statement of the grounds of rejection to be reviewed on appeal is correct except for the withdrawn rejection set forth below.

**WITHDRAWN REJECTIONS**

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.:

The rejection of Claims 64 and 65 as being anticipated by U.S. Patent No. 5,762,937.

The rejection of Claim 54 as being obvious over U.S. Patent No. 4,086,142 in view of U.S. Patent No. 4,736,020.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

TISCH, R. et al., *Proc. Natl. Acad. Sci. USA* 91:437-438, 1994.

LENMARK, A. *J. Int. Med.* 240:259-277, 1996.

HARRISON, L.C. *Molec. Med.* 1(7):722-727, 1995.

ATKINSON, M.A., et al. *Nat. Med.* 5(5):601-604, 1999.

PETERSEN, J.S., et al. *Autoimmunity*. 25 :129-138, 1997.

MARKETLETTER, *Marketletter Pubs Ltd*. September 13, 1999.

GOODNOW, C.C. *Lancet*. 357:2115-2121.

ATKINSON, M.A., et al. U.S. Patent No. 5,762,937, June 9, 1998.

HUANG, C.Y., et al. U.S. Patent No. 4,086,142, April 25, 1978.

HILLEN H. et al. U.S. Patent No. 4,736,020, April 5, 1988.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 31, 50-53, and 62-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for inhibiting the development of IDDM in a NOD mouse comprising administering GAD,

does not reasonably provide enablement for:

a method for inhibiting or preventing the development of IDDM in a patient comprising administering GAD, or a fragment thereof.

The goal of peptide irnmunotherapy of T-cell-mediated autoimmunity is to induce anergy in self reactive T cells. Therefore, the pathologies of autoreactive T cells in autoimmunity can be blocked by using the appropriate autoantigen or autoantigen-derived peptides (see Tisch, et al., *Proc. Natl. Acad. Sci. USA*. 91:437-438, 1994), page 437, col. 1, in particular). However, the effectiveness of this therapy hinges on several factors: one is whether the therapy can be used to treat an ongoing autoimmune response or whether it is useful only in preventing the disease. Typically, an autoimmune disease is diagnosed at the time of onset when significant tissue damage has already occurred. The onset of IDDM is not predictable and therefore, prophylaxis of these diseases is not currently possible; currently, therapy is initiated in these conditions only after the onset of disease symptoms. Furthermore, Tisch et al. (1994) teach that treating an ongoing T-cell-mediated autoimmunity by administering an antigen peptide may have an immunizing effect and exacerbate the disease condition (Tisch et al. (1994), page 437, column 3, in

particular). How the antigen is administered is also a key factor in determining whether an immunogenic or tolerogenic response is induced. The duration of the toleragenic effect is an additional factor. Frequent treatment over a prolonged period of time may result in unforeseen immunological complications. Furthermore, the Applicant discloses on page 20, lines 16-19, that "care should be taken that administration of the pharmaceutical compositions of the present invention does not potentiate the autoimmune response." There is a lack of guidance in the specification as to how the potentiation of the autoimmune response would be prevented using the instant invention. Additionally, the high degree of specificity required for the process of clonal deletion/anergy may be limiting when dealing with diseases such as MS, IDDM and rheumatoid arthritis, in which there are responses to several antigens ((Tisch, et al. (1994)), see page 437, col. 2 ¶ 3 and bridging over to col. 3, ¶ 4). Additionally, Lenmark (*J. Int. Med.* 240:259-277, 1996) teaches that "The mechanisms of GAD65-induced protection of spontaneous diabetes is critical to our understanding of autoimmune diabetes. Further experiments also extended to the spontaneously diabetic BB rat are warranted to determine the mechanism of protection, especially as other investigators have not found the published procedures to be easily reproducible." Lenmark (1996), see page 274, col. 2, paragraph 1, in particular). Additionally, Harrison (*Molec. Med.* 1:722, 727, 1995) teaches that "Insulin and GAD are strong candidate tolerogens for the prevention of human IDDM. However, caution should be exercised with GAD because, unlike insulin, it is not β cell specific and is found in high concentrations in the brain as well as in peripheral tissues other than islets.

Without further animal studies and knowledge of the GAD epitopes that elicit T cell reactivity unique to human β cells, it would seem unwise to manipulate immunity to this widely distributed key enzyme. For the present, insulin (or proinsulin) is the only islet antigen that, both on scientific and ethical grounds, justifies therapeutic application to humans at risk of IDDM." (Lenmark, 1996), see page 724, col. 2, paragraph 2, in particular). Applicant has provided only *in vitro* experiments demonstrating the identity of GAD in rat islets of Langerhans and in rat brain, and anti-GAD antibodies in the sera of patients with IDDM and stiff man syndrome, to demonstrate operability of the claimed polypeptide. Since humans and rats display different major histocompatibility complex haplotypes and Applicant has given no guidance as to how their peptide specific therapy would overcome autoreactive T cell escape mechanisms in humans or whether the peptide would induce autoimmunity or tolerance, it would require an undue amount of experimentation to one of skill in the art to practice the claimed invention.

Further regarding the breadth of the instant claims, none of the claims recite any limitation on the species or strain of the encompassed patient. It is noted, however, that essentially all of the enabling post-filing data (the specification discloses no data in support of the efficacy of the method of the instant claims) was collected using a single inbred animal model, i.e., the NOD mouse. As taught by Atkinson et al. (1999, of record) because the NOD mouse is a highly inbred strain, all experimental animals being genetically identical, results obtained employing said mouse should properly be viewed as

results more equivalent to "a single case study in humans," (page 602, column 1). Accordingly, care must be taken in attempting to extrapolate results obtained with the NOD mouse as encompassing all patients. Of record is the reference of Petersen et al. (1997) which specifically teaches that the method of the instant claims does not work in BB rats (*Treatment With GAD65 or BSA Does Not Protect Against Diabetes in BB Rats*). Clearly then the method of the instant claims is not enabled as broadly recited and the post-filing data offered in support of the method of the instant claims cannot enable the claims as broadly recited. Further, *no* evidence of record teaches the absolute prevention of the development of IDDM as recited in claim 62, but rather only the delay of disease in a highly artificial animal model. It must also be noted that the recitation of a GAD fragment in Claims 62-63 would encompass fragments as small as single amino acids, the administration of which for the inhibition of IDDM would be highly unpredictable.

Further note that more recent attempts to induce tolerance in humans have been completely unsuccessful in at least two different instances. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Finally note that a further recent reference (Goodnow, 2001) flatly states that tolerance induction is unpredictable as many tolerogenic antigens provide both signals that can be both tolerogenic and immunogenic.

Finally, Applicant argues that the BB rat model may be less reliable than the NOD mouse model as a predictor of efficacy in humans. It is unclear then why Applicant has employed a rat experimental model exclusively in the instant specification.

2. Claim 31 is rejected under 35 U.S.C. 102(e) as being anticipated by Atkinson (U.S. Patent No. 5,762,937).

The '937 patent teaches a method for inhibiting the development of IDDM comprising the administration of GAD to a patient, see col. 4, lines 40-48 and col. 25 line 53 and bridging over to col. 26, line 14. The administration of a therapeutically-effective dosage is inherent in the successful treatment of any disease.

Therefore, the reference teachings anticipate the claimed invention.

3. Claims 35, 49, and 54-57 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,762,937.

the '937 patent teaches a composition comprising GAD (see particularly, Example 14). Note that as said composition is clearly intended for *in vivo* administration, i.e., it is referred to as a vaccine, said composition would inherently comprise a pharmaceutically acceptable carrier. The reference further teaches a method for inhibiting the development of IDDM comprising administering lower molecular weight GAD (see particularly Claim 1). Note that lower molecular weight GAD is

the only GAD used by the reference, thus, said GAD would inherently be the GAD of the method of the claim.

The reference clearly anticipates the claimed invention.

4. Claims 35, 50-53, 59, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,762,937.

While the reference does not teach the claimed dosage limitations of 1-500 mg/kg patient body weight, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the dosage of the GAD administered in the method of the reference, said optimization falling well within the purview of one of skill in the art at the time of the invention. Claims 50-52 recite the only well-known sources of protein, i.e., recombinant, synthesized, and natural purified, accordingly it would have fallen well within the purview of one of skill in the art at the time of the invention to obtain the GAD employed in the claimed method from the only three known sources. Additionally, as the point of inhibiting the development of IDDM would have been to keep a patient from developing said disease, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of the claims on a prediabetic, i.e., a patient presumably likely to develop the disease, patient (as recited in Claim 53). Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform the method of the claims employing human GAD65 as said GAD is the actual

asserted autoantigen thus it would clearly be preferable to induce a tolerance to the actual antigen. Further, it would have been well-known to one of skill in the art at the time of the invention that human GAD65 would be incapable of inducing a xenogeneic response which could occur if a GAD65 from another species was used, again rendering human GAD65 the most preferred and accordingly, obvious.

5. Claims 35 and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,086,142 in view of U.S. Patent No. 4,736,020.

The '142 patent teaches a composition in a pharmaceutically acceptable carrier comprising GAD (see particularly, column 4, lines 14-16). Note that GAD comprises the same chemical composition regardless of source.

The reference teaching differs from the invention of the instant claims only in that the composition of the reference is not at least 99% w/w/ pure.

The '020 patent teaches the purification of a polypeptide to a purity of at least 99% (see particularly Examples I, 3, and 5). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce a GAD that was at least 99% w/w/pure, as taught by the combined '142 and '020 patents. One of ordinary skill in the art at the time the invention was made would have been motivated to produce said purified polypeptide as the purification of polypeptides to said purity was well-known in the art and it would generally be

considered more preferable to use more pure reagents. Thus, the addition of a new limitation to the claims requiring 99% purity of the claimed GAD polypeptide does not render the invention of the instant claims patentably distinct.

**(10) Response to Argument**

1. Appellant cites several references as showing "that administration of GAD to an animal model of IDDM, a NOD mouse, is effective to inhibit IDDM" and further states that "A phase-II clinical trial has confirmed safety and shown statistically significant evidence of efficacy in a patients with Late Autoimmune Disease in Adults (LADA), a subset of diabetes masquerading as type II on account of its late onset but which is now regarded as a form of Type 1 diabetes (see Baekkeskov declaration at paragraph (6) and Press Release attached to supplemental communication of July 22, 2003)".

Regarding the treatment of IDDM in the NOD mouse, said treatment is conceded. However, prevention of IDDM in the NOD mouse is not. Further, it is the treatment of IDDM in humans that is at issue. Regarding Appellant's second assertion, there in no supplemental communication dated July 22, 2003 in this application. The Inventor's declaration of May 23, 2003 did however state that results of a phase II trial would be released later in the year. Indeed the Inventor stated said results "may provide an indication of the efficacy of the vaccine in preventing patients from becoming insulin dependent". Thus, the current application contains none of the "statistically significant evidence of efficacy" asserted by Appellant.

Appellant cites *In re Brana*.

While Appellant provides an unusual position on the case, it is the Examiner's position that the holdings in a product case do not readily relate to the claims in the instant method case wherein the scope of enablement requirements, i.e., the specification need provide enablement for the full scope of the claimed method.

Appellant argues that it is the Inventor's opinion that the NOD mouse model is reasonably predictive of results in humans.

The Inventor's opinion is noted. As set forth in the rejection, results obtained employing the NOD mouse model must be viewed with caution. Additionally, as set forth in the rejection, the NOD mouse model was *not* employed in the experiments set forth in the instant specification.

Appellant again asserts, "and the phase II trial has provided statistically significant evidence of efficacy".

This assertion is not supported by the evidence in the instant application.

Appellant acknowledges that a phase I trial cannot establish efficacy, but asserts that "the fact that a phase I trial has been allowed to occur is an indication that a disinterested body of experts (i.e., the FDA or equivalent in other countries) has concluded from the relevant preclinical data including animal models, such as those in the references

cited in the Baekkeskov declaration at paragraph (5)), that the trial has a reasonable chance of success. This unsolicited and disinterested opinion of experts in the field stands in opposition to the office action's own assessment of the animal models".

As set forth previously, an attorney's assertions regarding the possible motivation of unknown experts does not comprise convincing evidence.

Appellant asserts results of a "successful phase II trial", "successful phase I and phase II trials have been completed", "successful clinical trials using GAD in a subset of patients undergoing autoimmune attack of GAD", etc.

As *no* such results are of record in the instant case said asserted results will not be addressed here no matter the number of times they are reasserted.

Appellant cites a textbook by Benjamini and Leskowitz (1988) in support of the claimed method of inducing tolerance.

Appellant's citing of a rudimentary text teaching that low or high doses of an antigen favor tolerance whereas intermediate doses favor an immunogenic response cannot be considered enabling for a method of manipulating one of the most complex physiological processes known. The attempted induction of immune tolerance has been the search for the holy grail of autoimmune immunologists for at least two generations. The

references set forth in the rejection teach that said grail has not yet been found.

Appellant argues that regarding the recitation of "preventing" and "fragment" of GAD, said terms have been allowed in similar claims. Additionally, the "fragment" of GAD is further defined by function, i.e., it must prevent or inhibit the development of IDDM.

The Examiner cannot comment on claims allowed nearly a decade ago nor what terms might have been acceptable then that are not now. Regarding the GAD fragments of the claims, no such fragments are disclosed, none are disclosed in the prior art of record, and it remains the Examiner's position that none are enabled.

Appellant argues that prevention does not imply absolute prevention.

The term most certainly encompasses absolute prevention and said prevention is not enabled by the instant specification.

Appellant concludes by asserting that the Examiner has not met his burden in establishing a lack of enablement.

It is the Examiner's position that the evidence of record clearly establishes the unpredictability of the method of the instant claims. The Examiner has provided numerous references detailing the difficulties involved in attempting to establish immune tolerance. Additionally, the Examiner has provided

references detailing the caution with which results obtained employing animal models of autoimmunity must be viewed when said results are intended as models of results that would hopefully be obtained in humans. A review of the actual application reveals that the application provides essentially no enablement for the instant claims. Only a few sentences are devoted to the method of the instant claims. Such a disclosure cannot be considered to be enabling for a method that was not, and still is not, routine as Appellant's arguments and assertions might suggest.

Finally note that should the induction of immune tolerance someday become routine in humans, said future findings cannot enable the claimed method with a priority date of 1990.

A set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of sufficient working examples, i.e., the specification discloses *no* data representative of the method of the instant claims, the unpredictability of the art, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

2. Appellant does not dispute the merits of the rejection of Claims 33, 64, and 65 as being anticipated by the '937 patent.

3. Appellant does not dispute the merits of the rejection of Claims 35 and 55-57 as being anticipated by the '937 patent. Appellant argues that Claim 54 is not anticipated by said patent. Specifically, Appellant argues that while the GAD of Claim 35 is taught by the prior art, the lower molecular weight form alone is not. Appellant argues that lower molecular weight form would be difficult to purify.

As set forth in the rejection, the lower molecular weight form of GAD is the form of the '937 patent (note that it is clearly differentiated from the higher molecular weight 67kD form at, for example, Example 6). Thus, if the reference anticipates the GAD of Claim 35, as conceded by Appellant, then it must also anticipate the GAD of Claim 54. Regarding the purification of said GAD, the instant specification at page 14 discloses that said protein can be purified by "conventional protein purification techniques".

4. Appellant does not dispute the merits of the rejection of Claims 50-53, 66, and 77 as being obvious in view of the '937 patent. Appellant argues that Claim 59 is not obvious in view of said patent. Specifically, Appellant argues that lower molecular weight form would be difficult to purify and that the reference does not teach two forms of GAD.

As set forth above, the instant specification at page 14 discloses that GAD's can be purified by "conventional protein purification techniques". And as set forth above, the reference clearly distinguishes the lower molecular weight form of GAD from the higher 67kD form of GAD. Note that Appellant cites Kobayashi et al. (1987) but that said reference has not been cited in the Evidence Appendix. In the interest of compact prosecution the Brief has not been considered to be defective but said reference will not be addressed.

5. Appellant argues that "neither the feasibility of purifying proteins to 99% nor the general preference for use of pure reagents would have provided sufficient motivation to combine the teachings of the references".

Regarding feasibility, the specification makes clear that protein purification to at least 99% was routine in the art "using conventional protein purification techniques". The '020 patent merely affirms the specification in establishing the desirability of 99% pure proteins.

Appellant argues that the GAD of the '142 patent is not suitable for parenteral use in a human and that the GAD of the references is not the GAD of Claims 55-57.

The GAD of the reference was purified in a buffer in which its enzymatic activity was maintained, thus demonstrating that the preparation was not incompatible with biological use. Regarding the GAD of Claims 55-57, the application contains no evidence that the GAD prepared by any particular technique comprises a different GAD than would be prepared by the purification method of the combined references.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the Examiner in the Related Appeals and Interferences section of this Examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,
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3/16/04
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PRIMARY EXAMINER

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